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Case Report

Case Report

Oncocytic Adrenocortical Carcinoma With Low ^{18}F-FDG Uptake and the Absence of Glucose Transporter 1 Expression

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Abbreviations: ACC, adrenocortical carcinoma; ACTH, adrenocorticotropic hormone; CT, computed tomography; DHEA, dehydroepiandrosterone; DHEA-S, dehydroepiandrosterone sulfate; ENSAT, European Network for the Study of Adrenal Tumors; FDG, ^{18}F-fluorodeoxyglucose; GLUT1, glucose transporter 1; HDL, high-density lipoprotein; HU, Hounsfield unit; LDL, low-density lipoprotein; MRI, magnetic resonance imaging; PET, positron emission tomography; SUV, standardized uptake value.

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Abstract

Adrenocortical carcinoma (ACC) is a rare tumor, and some histological variants (oncocytic, myxoid, and sarcomatoid ACCs) have been reported in addition to the conventional ACC. Among these subtypes, oncocytic ACC is histologically characterized by the presence of abundant eosinophilic granular cytoplasm in the carcinoma cells owing to the accumulation of mitochondria, which generally yields high ^{18}F-fluorodeoxyglucose (FDG) uptake on positron emission tomography (PET). Herein, we report the case of a 21-year-old woman with oncocytic ACC with low FDG uptake on PET scan. Her circulating levels of androgens were high, and androgen-synthesis enzymes were detected in carcinoma cells. The patient also had hypocholesterolemia. However, glucose transporter 1 (GLUT1) was not detected in the tumor, which was considered to account for the low FDG uptake by the tumor. To the best of our knowledge, this is the first case of low FDG uptake by oncocytic ACC without GLUT1 expression. Additionally, since hypocholesterolemia was reported in 3 previous reports of androgen-producing tumors, a possible correlation between androgenicity in adrenal tumors and the development of hypocholesterolemia could be postulated; however, further investigations are needed for

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clarification. This case highlights important information regarding the diversity of ACC and its impact on hypocholesterolemia.

Keywords: adrenal incidentaloma, androgen, cholesterol, DHEA-S, ENSAT, SUVmax

Adrenocortical carcinoma (ACC) is a rare malignancy with an annual worldwide incidence of 0.5–2 cases per million population [1]. Apart from the conventional ACC, some histological variants (oncocytic, myxoid, and sarcomatoid ACCs) have been characterized in the latest World Health Organization classification [1, 2]. Oncocytic ACC is histologically characterized by tumor cells with abundant eosinophilic granular cytoplasm, reflecting the accumulation of mitochondria [1–3].

Positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose (FDG) has been used to clinically detect various malignant lesions. ACC has been reported to harbor markedly increased FDG uptake, surpassing the liver background [4]. Even in the case of benign adrenocortical tumors, adrenocortical oncocytoma has been reported to be associated with increased FDG uptake owing to the presence of numerous intracellular mitochondria [5] and increased glucose transporter 1 (GLUT1) expression [6]. Herein, we report a rare case of oncocytic ACC with low FDG uptake. To the best of our knowledge, no similar case has been reported previously. GLUT1 expression was very low in the tumor, which could account for the decreased FDG uptake. Additionally, marked hypocholesterolemia was observed in the patient. Only 3 cases of hypocholesterolemia associated with adrenal tumors have been reported in the English literature [7-9], and these concomitant cases will be discussed.

Case Presentation

A 21-year-old Japanese woman was referred to our hospital for the characterization of a left adrenal tumor, which was incidentally detected on abdominal computed tomography (CT) after a traffic accident. The oval-shaped tumor measured 7.7 × 4.5 cm^2 and had a homogeneous density of 40 Hounsfield units (HU) on a plain CT scan (Fig. 1A).

The patient underwent a detailed endocrine examination. She was aware of secondary amenorrhea since the age of 20 years; however, she had not paid any particular attention to it. She had no symptoms associated with excess hormone levels in the adrenal cortex or medulla, including hirsutism, and no medical history. Physical examination revealed no significant findings. Clinical parameters were as follows: body height, 162 cm; body weight, 54.0 kg; blood pressure, 110/58 mmHg; and heart rate, 71 beats/minute.

Laboratory data at the time of admission are summarized in Table 1. The complete blood count and blood biochemistry tests were within the normal range, except for extremely low serum total, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) cholesterol levels. As for the endocrine findings, blood and 24-hour urine catecholamine levels were within the normal range. Plasma aldosterone concentration was high (438 pg/mL); however, plasma renin activity of 2.2 ng/mL/h and aldosterone/renin ratio of 199 were within the normal range; these values may reflect a reduction in salt intake after hospitalization relative to before. Cortisol and adrenocorticotropic hormone (ACTH) levels early in the morning were 10.4 μg/dL and 73.0 pg/mL, respectively. Serum dehydroepiandrosterone (DHEA)-sulfate (DHEA-S), testosterone, and urine 17-ketosteroid levels, especially at the DHEA level, were extremely high, which indicated an excess of adrenal androgens. Because a large adrenal mass was found, the patient underwent an overnight 1 mg dexamethasone suppression test. The cortisol level was 1.7 μg/dL, which ruled out the autonomous secretion of cortisol.

Magnetic resonance imaging (MRI) revealed a left mass measuring 7.2 × 4.6 cm^2 (Fig. 1B-1E). The tumor showed a clear margin and isointense signal on T1-weighted images and iso- to hyperintense on T2-weighted images (Fig. 1B and 1C). On chemical shift MRI of the adrenal glands, the loss of signal intensity was not detected in out-of-phase imaging when compared with that of the spleen (Fig. 1D and 1E). On FDG-PET (Fig. 1F), the maximum standardized uptake value (SUVmax) of the left adrenal tumor was 2.8, and the adrenal to liver SUVmax was 0.98. There were no signals detected anywhere that would make us suspect a malignant tumor.

The patient underwent laparoscopic left adrenalectomy. The resected left adrenal gland weighed 130 g, and the tumor measured 82 mm × 50 mm × 50 mm. Representative histological findings are presented in Fig. 2. The tumor cells contained abundant eosinophilic cytoplasm (Fig. 2A). Capsular and sinusoidal invasions were not identified, and the normal adrenal cortex was detected in a compressed fashion near the capsule. Nuclear atypia (Fig. 2B) and a high mitotic index were detected with a diffuse growth pattern (Fig. 2C). The patient's Weiss score was 4, and the tumor met a major criterion for the Lin-Weiss-Bisceglia system. The Ki-67 labeling index was 6% at hot spots (Fig. 2D). Tumor cells were immunopositive for steroidogenic

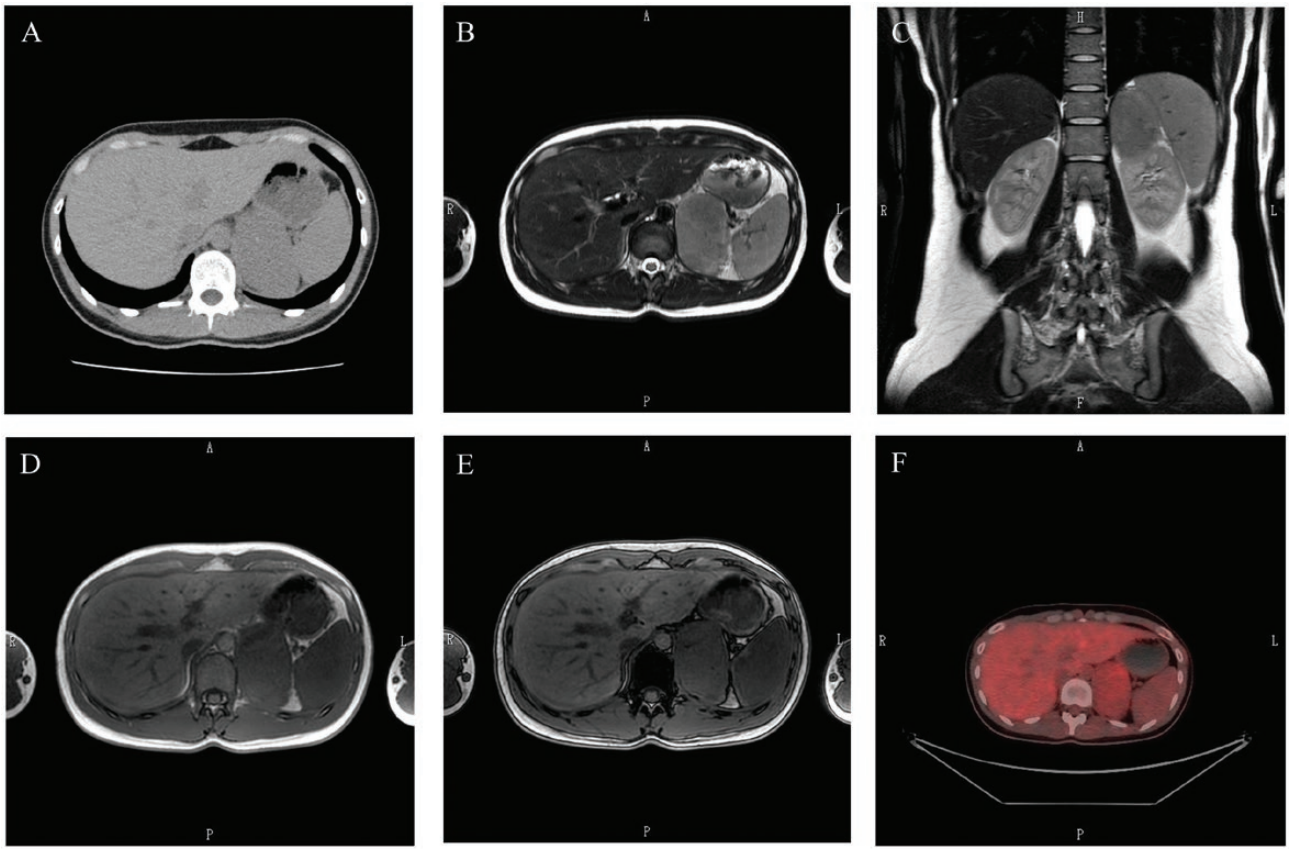

Figure 1. (A) Plain computed tomography (CT) scans of the left adrenal area, showing a tumor with clear borders measuring 7.7 × 4.5 cm^2. (B–E) Magnetic resonance imaging (MRI). T2-weighted images (B, C) and images in-phase (D) and out-of-phase (E) using chemical shift MRI. (F) Positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose (FDG). The maximum standardized uptake value (SUVmax) of the left adrenal tumor was 2.8, and the adrenal to liver SUVmax was 0.98.

factor 1 (Fig. 2E), indicating a tumor of the adrenal cortex. Tumor cells were diffusely and intensively immunopositive for mitochondria (Fig. 2F), indicating an oncocytic tumor. To evaluate steroid synthesizability in the resected tumor, we immunohistochemically evaluated the expression of steroidogenic enzymes (Fig. 3). The tumor cells were immunohistochemically positive for steroidogenic acute regulatory proteins (StAR), 21-hydroxylase, 11β-hydroxylase (CYP11β1), 17α-hydroxylase, DHEA-sulfotransferase, and 17β-hydroxysteroid dehydrogenase 5. The tumor was negative for 3β-hydroxysteroid dehydrogenase and 18-hydroxylase (CYP11β2). These results demonstrated that tumor cells produced DHEA and DHEA-S, but not cortisol and aldosterone. The final diagnosis was oncocytic ACC with an androgen-producing ability.

These results led to a new question: why was this tumor negative on FDG-PET? We hypothesized that glucose uptake in this tumor could be suppressed, and immunostaining for GLUT1, which is usually highly expressed in oncocytic ACC, revealed no immunoreactivity in the tumors (Fig. 4).

The postoperative course of the patient was unremarkable. Amenorrhea, which was the only symptom of androgen excess, improved after surgery. Postoperative steroid treatment was not required. Mitotane was not administered because of the low-grade nature of the ACC. Postoperative blood cortisol and ACTH levels early in the morning were 6.7 μg/dL and 27.7 pg/mL, respectively. Plasma aldosterone concentration of 73.6 pg/mL, plasma renin activity of 0.8 ng/mL/h, and aldosterone/renin ratio of 92 were within the normal ranges. Serum DHEA-S level regressed to 293 μg/dL and testosterone level to 0.35 ng/mL. Serum total cholesterol, triglyceride, HDL-cholesterol, and LDL-cholesterol levels were 142 mg/dL, 44 mg/dL, 51 mg/dL, and 82 mg/dL, respectively, which were within the normal ranges. At 1 year postoperatively, there were no signs of ACC recurrence.

Discussion

A large left adrenal tumor measuring >7 cm was incidentally detected in our patient. The tumor showed a density of approximately 40 HU on a CT scan. Our case was of a functional tumor, but even if it was a nonfunctional tumor, consideration of surgery would have been appropriate. In

Table 1. Laboratory findings of the patient

Peripheral blood			**Endocrinological data (plasma or serum)**		
WBC	5370/mm^3	(3300–8600)	Epinephrine	43 pg/mL	(0–100)
RBC	486 × 10^4/mm^3	(386–492)	Norepinephrine	159 pg/mL	(100–450)
Hemoglobin	14.7 g/dL	(11.6–14.8)	Dopamine	6 pg/mL	(0–20)
Hematocrit	41.7%	(35.1–44.4)	Renin activity	2.2 ng/mL/h	(0.3–5.4)
Platelets	22.4 × 10^4/mm^3	(15.8–34.8)	Aldosterone	438 pg/mL	(29.9–159)
			ARR	199	(<200)
Biochemical data			ACTH	73.0 pg/mL	(7.2–63.3)
Total protein	6.5 g/dL	(6.6–8.1)	Cortisol	10.4 μg/dL	(6.2–19.4)
Albumin	4.2 g/dL	(4.1–5.1)	DHEA-S	4060 μg/dL	(18–391)
Total bilirubin	1.1 mg/dL	(0.4–1.5)	Testosterone	3.51 ng/mL	(0.11–0.47)
AST	13 U/L	(13–30)			
ALT	9 U/L	(7–23)	**Endocrinological data (urine)**		
LDH	168 U/L	(124–222)	Epinephrine	4.0 μg/day	(3.4–26.9)
ALP	189 U/L	(106–322)	Norepinephrine	45.1 μg/day	(48.6–168.4)
rGTP	7 U/L	(9–32)	Metanephrine	0.09 mg/day	(0.04–0.19)
BUN	10 mg/dL	(8–20)	Normetanephrine	0.09 mg/day	(0.09–0.33)
Creatinine	0.72 mg/dL	(0.46–0.79)	(17-ketosteroid fraction)		
Natrium	142 mEq/L	(138–145)	Androsterone	22.44 mg/day	(0.4–3.0)
Potassium	4.1 mEq/L	(3.6–4.8)	Etiocholanolone	23.42 mg/day	(0.3–2.5)
Chlorine	105 mEq/L	(101–108)	Dehydroepiandrosterone	493.86 mg/day	(0.04–2.6)
Glucose	78 mg/dL	(73–109)	11-ketoandrosterone	0.70 mg/day	(0.0–0.07)
T.chol	47 mg/dL	(142–220)	11-ketoetiocholanolone	1.32 mg/day	(0.03–0.5)
Triglyceride	32 mg/dL	(30–150)	11-OH androsterone	8.42 mg/day	(0.22–1.6)
HDL-c	32 mg/dL	(40–103)	11-OH etiocholanolone	0.53 mg/day	(0.02–0.65)
LDL-c	9 mg/dL	(65–140)			
sIL-2R	243 U/mL	(121–613)			

Reference ranges are in parentheses.

Abbreviations: ACTH, adrenocorticotropic hormone; ALP, alkaline phosphatase; ALT, alanine transferase; ARR, aldosterone/renin ratio; AST, aspartate transaminase; BUN, blood urea nitrogen; DHEA-S, dehydroepiandrosterone sulfate; HDL-c, high-density lipoprotein-cholesterol; LDH, lactate dehydrogenase; LDL-c, low-density lipoprotein-cholesterol; RBC, red blood cells; rGTP, γ-glutamyl transferase; sIL-2R, soluble interleukin-2 receptor; T.chol, total cholesterol; WBC, white blood cells.

some papers, tumors measureing >4 cm [11, 12] should be considered for surgery; in others, tumors measureing >4.6 cm or with an attenuation of >20 HU on CT scan [13], should be considered for surgery, because of the possibility of malignancy. On chemical shift MRI of the adrenal glands, the loss of signal intensity was not detected on out-of-phase imaging when compared with that of the spleen, suggesting the possibility of malignancy rather than adenoma [14]. The FDG-PET scan was negative in our case; however, adrenalectomy was performed because the tumor was functional, and imaging findings other than the FDG-PET scan were suspicious for carcinoma.

The pathological diagnosis after surgery was oncocytic ACC. Weiss's criteria are considered the gold standard criteria for diagnosing ACC, with a combined score of ≥3 considered as malignancy [1, 2]. In our patient, the following 4 criteria were met: high nuclear grade, <25% of clear cells, diffuse architecture, and high mitotic index. Because the first 3 of Weiss's criteria are characteristic of oncocytic neoplasms, Weiss's criteria could result in the overdiagnosis during the pathological diagnosis of oncocytic ACC; hence, it may be better to use the Lin-Weiss-Bisceglia system [1, 2, 15]. In our patient, 1 major Lin-Weiss-Bisceglia criterion, a high mitotic index, was met, indicating malignancy. However, the differentiation between benign and malignant adrenal oncocytic tumors in pathological diagnosis remains controversial.

FDG-PET is useful for the differential diagnosis of benign and malignant lesions. Several studies on adrenocortical neoplasms demonstrated that the cutoff values of SUVmax for adrenal lesions ranged from 2.5 to 5.2, and the cutoff value of adrenal to liver SUVmax ratio ranged from 1.53 to 1.8 [16-19]. However, it is also true that the patients included in those studies were diagnosed with metastatic adrenal carcinoma. Owing to the rarity of ACC, little evidence exists for the cutoff values. Groussin et al reported that in a study of 22 ACC cases and 43 adrenocortical adenoma cases, using a cutoff value of >1.45 for the adrenal to liver SUVmax ratio could differentiate between ACC and adrenocortical adenoma [4]. In the same study, an SUVmax

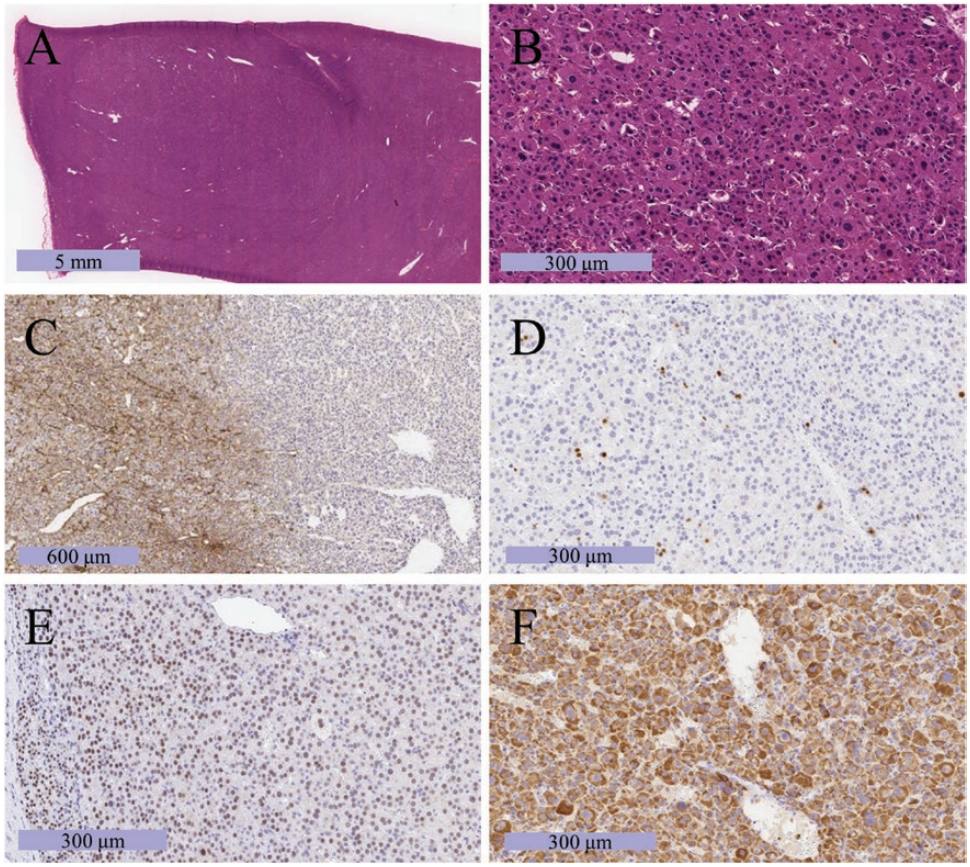

Figure 2. Photomicrograph of the resected tumor. (A, B) Hematoxylin and eosin staining in low-power (A) and high-power (B) fields. (C) Immunohistochemical labeling for type IV collagen, which can confirm the presence of diffuse proliferation by checking whether the basic chordal structure has been destroyed or not. (D) Immunohistochemical labeling for Ki-67, which can stain cell nuclei during all active phases of the cell cycle and is used as a marker of cell proliferation. The Ki-67 labeling index was 6%. (E) Immunohistochemical labeling for SF-1, which can stain cell nuclei derived from steroidogenic hormone-producing glands such as the adrenal cortex [10]. (F) Immunohistochemical labeling for mitochondria. In the case of the oncocytic tumor, mitochondrial staining can be observed throughout the cytoplasm.

cutoff value of >3.4 for adrenal lesions was also proposed [4]. Tessonnier et al reported that 37 patients with ACC harbored median uptake values of SUVmax = 11 (range, 3-56) on FDG-PET scans [20]. In our patient, the SUVmax for the left adrenal tumor was 2.8, and the adrenal to liver SUVmax was 0.98. Therefore, this tumor was considered benign on FDG-PET scans, contrary to the malignant findings in the pathological diagnosis.

One major question in our case was the extremely low FDG uptake despite the presence of oncocytic ACC. Most aggressive malignant tumors, such as ACC, are known to utilize aerobic glycolysis to derive a substantial amount of energy [21]. Therefore, a large amount of glucose is usually taken up by malignant cells. Labeled deoxy-glucose, which is a glucose analog used in FDG-PET, enters the cell through specific transmembrane carrier proteins, especially GLUT1 [22]. Even in the case of benign tumors, oncocytic tumors such as those of the parotid gland, renal cells, adrenocortical cells, and thyroid Hurthle cells have been reported to be associated with increased FDG uptake [6, 21, 23, 24] owing to the presence of numerous intracellular mitochondria [5] and increased GLUT1 expression [6]. FDG uptake was expected to be high in our case considering the oncocytic nature of the lesion. Therefore, to further explore the pathogenesis of low FDG uptake in this oncocytic tumor, we hypothesized that tumoral glucose uptake could be suppressed, and proceeded to investigate GLUT1 expression. No immunoreactivity of GLUT1 was detected, which was one of the reasons for FDG-PET negativity. The reason for the decreased expression of GLUT1 in this tumor is unknown; however, it has been reported that GLUT1 expression is not always observed in conventional ACCs that are not oncocytic [25, 26]. Since no similar cases have been reported in the literature, additional reports of oncocytic ACC cases are needed to clarify this phenomenon.

Oncocytic ACC produced androgens in our patient. Because of the rarity of oncocytic ACC, there have been only a few reports; however, approximately one-third of oncocytic ACCs have been reported to produce androgens [27, 28]. To the best of our knowledge, ours is the

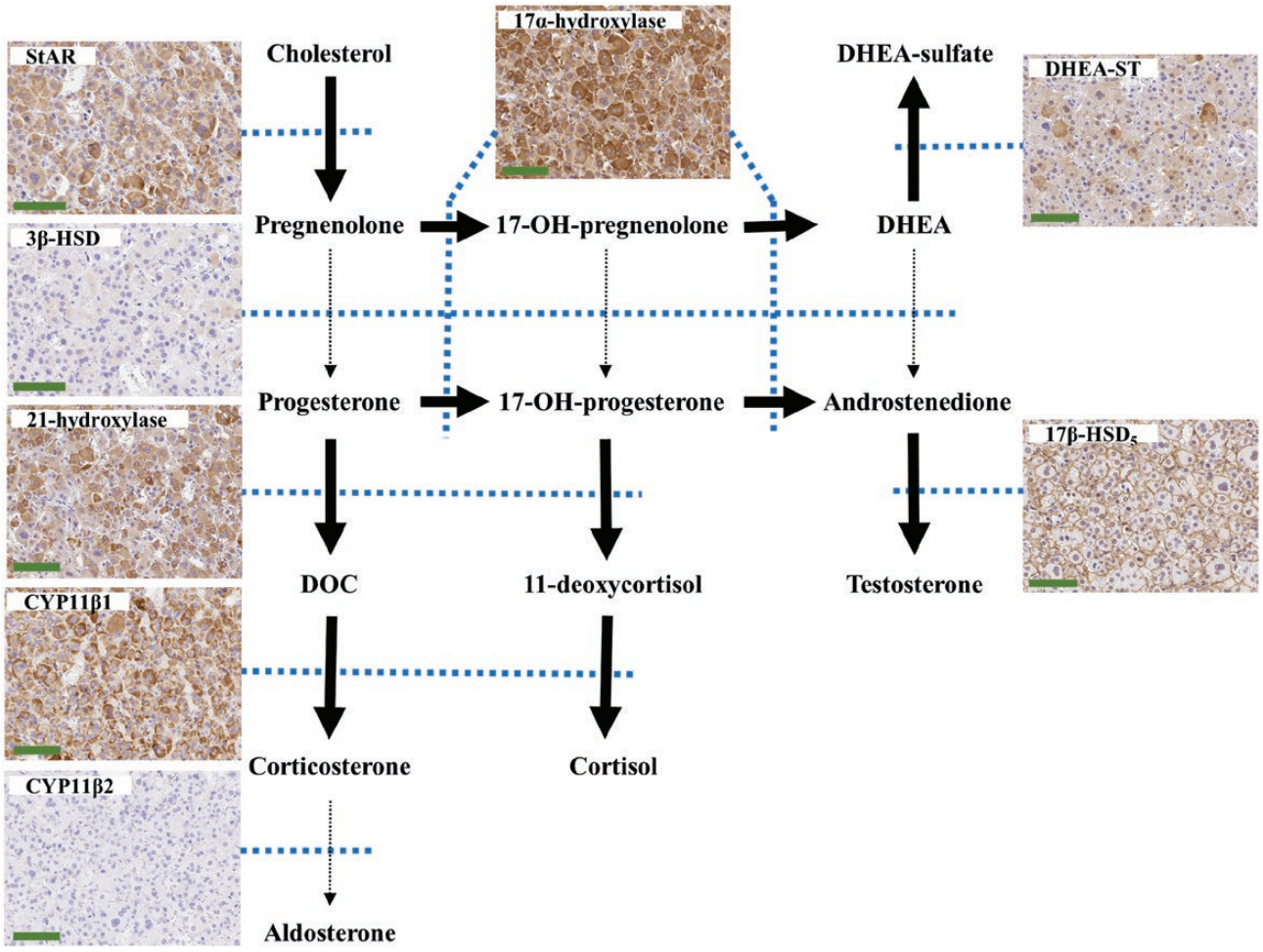

Figure 3. The steroid synthesis pathway and photomicrographs of immunohistochemical labeling of steroid synthases in the resected tumor. The tumor was positive for steroidogenic acute regulatory protein (StAR), 21-hydroxylase, 11β-hydroxylase (CYP11β1), 17α-hydroxylase, DHEA-sulfotransferase (DHEA-ST), and 17β-hydroxysteroid dehydrogenase (HSD) 5 (17β-HSD5). The tumor was negative for 3β-HSD and 18-hydroxylase (CYP11β2). Blue dotted lines show related enzymes. Bold arrows mean "convertible" because of the existence of related enzymes. Dotted arrows mean "difficult to convert" because of low-level related enzymes. Scale bar: 100 μm. Abbreviations: DHEA: dehydroepiandrosterone, DOC: deoxycorticosterone.

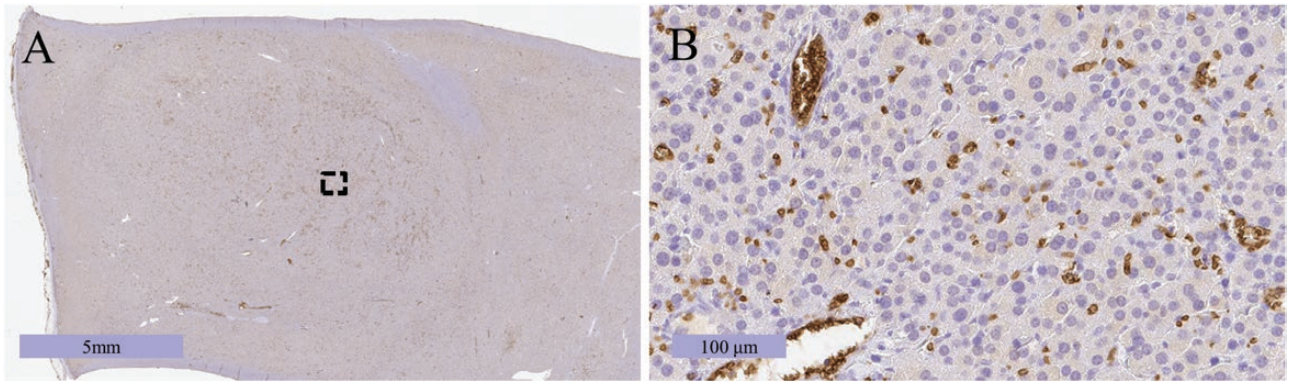

Figure 4. (A) Photomicrograph of the resected tumor stained for glucose transporter 1 (GLUT1). (B) Enlarged view of the dotted region in (A). The tumor cells were GLUT1-negative (positive cells were erythrocytes for inner positive control).

first report of a detailed analysis of the expression of steroidogenic enzymes in functional oncocytic ACC. The results revealed that the status of the enzymes in the tumor tissue and corresponding circulating hormone levels were consistent, which also confirmed the usefulness of immunohistochemical evaluation of steroidogenic enzymes

Table 2. Summary of case reports on hypocholesterolemia associated with androgen-producing adrenal tumors

Author, year (ref)	Age (year)	Gender	Symptom	Excess hormone	T.chol (pre-operation)	T.chol (post-operation)	Diagnosis, affected side, tumor size
Leichter & Daughada, 1974 [8]	48	Female	Hirsutism, amenorrhea	Androgen	95 mg/dL	185 mg/dL	Benign adenoma, right, 20 cm
Nakagawa et al., 1995 [9]	16	Female	Hirsutism, amenorrhea	Androgen, cortisol	23 mg/dL*	> 115mg/dL*	Benign adenoma, right, 10 cm
Benvenga, 1995 [7]	20	Female	Hirsutism, oligomenorrhea	Androgen, cortisol	30 mg/dL*	127 mg/dL*	Nonmalignant adrenal tumor, right, 15 cm
Present case	21	Female	Amenorrhea	Androgen	47 mg/dL	142 mg/dL	Oncocytic ACC, left, 8.2 cm

Abbreviations: ACC, Adrenocortical carcinoma; T.chol, total cholesterol; ref, reference.
*Values that had been reported in millimole per liter were converted to milligram per deciliter by dividing by 0.0259.

in exploring the features of neoplastic steroidogenesis in functioning adrenocortical tumors. Additionally, serum androgen levels decreased after surgery, and amenorrhea clinically improved. Recently, Harada et al reported a similar case of oncocytic ACC; however, it was nonfunctional [29], and neither PET results nor GLUT1 immunostaining were reported.

ACC is a rare tumor; thus, treatment decisions are difficult. However, the European Network for the Study of Adrenal Tumors (ENSAT) and the European Society of Endocrinology have published guidelines on the management of adrenocortical carcinoma in adults [30]. Before surgery, our case was evaluated as ACC amenable to complete resection (stage II according to the ENSAT staging system). Complete resection was performed, and the Ki-67 labeling index was <10%; therefore, the risk of recurrence was determined to be low/moderate. The guidelines above, however, did not necessarily mention that adjuvant mitotane therapy was always necessary but emphasized that the requirement of adjuvant mitotane therapy should be discussed on an individual basis. Our patient was not administered mitotane postoperatively because of the oncocytic nature of ACC, which was reported to have a better clinical outcome than conventional ACC [27, 28, 31]. Additionally, our case was GLUT1 negative. The higher expression of GLUT1 was associated with a worse prognosis in ACC; particularly, high GLUT1 expression in ACC indicated increased glucose uptake, which correlates with aggressive behavior [25, 26]. As expected, no recurrence was detected in our patient at this juncture, 1 year after the surgery. Long-term imaging and biochemical (eg, blood DHEA-S level) follow-up are warranted since the outcome and clinical behavior of GLUT1-negative oncocytic ACC remain uncertain.

In our patient, marked hypocholesterolemia was observed. To date, 3 similar cases have been reported in the English literature [7-9]. The clinical features and diagnoses of the 4 patients, including ours, are summarized in Table 2. In all these reports, the cases involved women, and serum androgen levels were high, similar to our study. However, the tumors were reported as benign adenomas, which is different from our case of the malignant tumor. The pathogenesis of hypocholesterolemia in patients with adrenal tumors has been reported to be subsequent to increased LDL receptor activity and unrestricted uptake of LDL by the adrenal tumor [9], but not the effect of increased serum levels of androgens on LDL receptors [9]. Because all 4 cases, including our case, showed high androgen levels, and because there have been no reports of hypocholesterolemia in patients with adrenal tumors other than androgen-producing tumors, we assume that androgen-producing tumors themselves could play a role in the development of hypocholesterolemia; however, further investigation is required for clarification.

In conclusion, we report the case of a patient with an oncocytic ACC with low ^{18}F-FDG uptake. Particularly, the ACC masquerades as a benign lesion on PET/CT scans, and immunohistochemical analysis indicated low GLUT1 expression in the tumor. Since there are no similar cases reported in the literature, additional case reports are needed to prove this phenomenon. Moreover, the presence of hypocholesterolemia with adrenal masses has been reported in 4 cases, including ours, all of which involved androgen-producing tumors. Therefore, a possible correlation between androgenicity in adrenal tumors and the development of hypocholesterolemia could be proposed; however, further investigation is warranted.

Additional Information

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Data Availability: Data sharing is not applicable to this article, as no datasets were generated or analyzed during the current study.

Consent for Publication: Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

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